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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,017	02/13/2002	Thomas E. Jenkins	P-009-RC2	8903

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EXAMINER	
SHIBUYA, MARK LANCE	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 09/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,017	JENKINS ET AL.	
	Examiner	Art Unit	
	Mark L. Shibuya	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *64-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64-68* is/are rejected.

7)☒ Claim(s) *65-68* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/30/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 64-68 are pending. Claim 64 is withdrawn from consideration, to the extent that claim 64 is drawn to unelected inventions.

Election/Restrictions

2. Applicant's election with traverse of Group in the reply filed on 8/17/2004 is acknowledged. The traversal is on the ground(s): that examination of all compounds defined in claim 64 would not constitute an undue burden; that In re Weber, 580 F.2d. 455, 458, 198 U.S.P.Q. 328, 331-332 (C.C.P.A. 1978) stands for the general proposition that if a single claim is required to be divided up and presented in several applications, that claim would never be considered on the merit; and that the examiner has not made, nor has he even attempted to make, a proper showing that the present claims lack unity of invention.

This is not found persuasive because claims 64-68 embrace a great multitude of independent molecular structures. For example, this can be seen from the group elected by the applicant that is drawn to –C(O)-alkylene-alkylene-C(O)-; wherein the term "alkylene" refers to a diradical of a branched or unbranched saturated hydrocarbon chain, preferably having from 1 to 40 carbon atoms. Many different molecular structures are embraced in this one group alone. The examiner respectfully submits that examination full scope of the vast multitude of different molecules embraced by the different groups of claim 64 in a single application would constitute an undue burden.

Furthermore, In re Weber, 198 U.S.P.Q. 328 at 332, states: "[w]e hold that a rejection under § 121 violates the basic right of the applicant to claim his invention as he

chooses." However, unlike the facts of In re Weber, instant claim 64, is *not rejected*, but *withdrawn*, in part, from consideration under 35 U.S.C. § 121. The examiner respectfully submits said withdrawal remains proper and that applicant's reliance upon In re Weber is inapropos because In re Weber is distinguished.

Finally, in the Requirement for Restriction/Election, mailed 7/23/2004, at bridging paragraph 3, pp. 3-4, the examiner stated:

> The inventions of claims 64-68, wherein library of test compounds are specifically defined as to **X', Z, Y', m, Y'', R', R'', and n**, are test compounds with structurally distinct core structures and so that they are unrelated each to the other. . . . Absent evidence to the contrary, test compounds with structurally distinct core structures are presumed to represent independent and distinct inventions, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.1141 et seq.

Requirement for Restriction/Election at pp. 3-4. The examiner respectfully reiterates that there is no common structure shared by the multitude of compounds embraced by claim 64. Applicant traverses this finding, but does not point to a common core structure found in all the molecules encompassed by claim 64. Thus restricted claims 64-68 lack unity of invention.

The requirement is still deemed proper and is therefore made FINAL.

Priority

3. Acknowledgement is made of applicant's claim that this application, filed 2/13/2002, is a continuation of U.S. Serial No. 09/499,176, filed on 2/7/2000, abandoned on 5/24/02; which is a continuation of U.S. Serial No. 09/327,096, filed on 6/7/1999, abandoned on 2/8/2000; which application claims the benefit of U.S.

Provisional Application Serial No. 60/088,465, filed 6/8/1998, and U.S. Provisional Application Serial No. 60/093,068, filed 716/1998.

Claim Objections

4. Claims 64-68 are objected to, in part, for depending from claim 64, which is withdrawn, in part, as drawn to non-elected method inventions comprising the formula: L-X-L, wherein X is other than –C(O)-alkylene-alkylene-C(O)-.

Claim Rejections - 35 USC § 112

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 64-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 64 (and its dependent claims) recites the limitations “a ligand compound” and "a cell membrane transporter" in line 20; the language “a linker compound” in line 26; and “a library of compounds” in line 32. There is uncertain antecedent basis for these limitations in the claim. The relationship of “a ligand compound”, and “a linker compound” to “a ligand” in line 4 and “a linker” in line 5, respectively, is uncertain. The relationship of “a library of compounds” to “a library of compounds” in line 1, is uncertain. Also it is unclear as to whether “a cell membrane transporter” in line 20 is the same as “a cell membrane transporter” in line 4.

Claim 65 recites the language "its affinity" in line 3; it is unclear as to whether it is the affinity of the "compound" or the "library" that is referred to.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 64-68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a *Written Description Rejection*.

Vas-Cath Inc. v. Mahurkar, 19 USPQ 2d 1111, 1117, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." The instant specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 116).

The skilled artisan cannot envision the detailed chemical structure of the encompassed genera of all ligands that bind to a cell membrane transporter or to cell membrane transporters that are ion channels or sodium ion channels, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description

requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The ligands themselves are required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, at 1483 (finding claims directed to *mammalian* FGF's were found to be unpatentable due to lack of written description for that broad class, where the specification provided only the *bovine* sequence).

Therefore, only the ligands that bind to a cell membrane transporter or to cell membrane transporters that are ion channels or sodium ion channels, as taught by the instant specification, but not the full breadth of the claim, meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

7. Claims 64-68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for ligands taught by the instant specification, does not reasonably provide enablement for all ligands that bind to a cell membrane transporter or to any cell membrane transporter that are ion channels or to any sodium ion channel. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether undue experiment is necessitated. These factors can include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the relative skill of those in the art;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1 and 2) The breadth of the claims and the nature of the invention: The claims recite methods for preparing a library of compounds comprising ligands which bind to a cell membrane transporter or to cell membrane transporters that are ion channels or to sodium ion channels. Step (a) of claim 63 is "identifying a ligand compound which binds to a cell membrane transporter". This step encompasses experimental discovery of new ligands to any membrane transporter. No other structural limitation for the ligands are recited by the claims, and as such, this could read on a vast variety of structures. Thus the claims are very broad in scope of encompassed subject matter.

(3 and 5) The state of the prior art and the level of predictability in the art: Methods for identifying a ligand that binds to cellular membrane transporters were known at the time of filing; however, only a limited number of ligands were known, given the broad range of cellular transport functions contemplated to be under control of

cellular membrane transporters. These fundamental cellular functions include transport of sodium, potassium, and chloride ions. Also included are transporters of amino acids, and other nutrients and essentials for the cell, neurotransmitters and various hormones, etc., for example. The structures of possible ligands are so diverse that one of skill in the art would not be able to predict such structures. Applicant's claimed scope of ligands for membrane transporters represents only an invitation to experiment (see also above concerning written description and cases cited therein).

(4) The level of one or ordinary skill: The level of skill would be high, most likely at the Ph.D. level. However, such persons of ordinary skill in this art, *given its unpredictability*, would have to engage in undue (non-routine) experimentation to carry out the invention as claimed.

(6-7) The amount of direction provided by the inventor and the existence of working examples: The Specification at p. 80, line 21 - p. 81, line 16, contemplates selecting any ligand capable of interacting with the target, and looks to known drugs as ligands from which to pick and choose. Applicants have provided examples of known drugs that can act as ligands for cellular transport proteins. However, the Specification does not disclose a single screening assay for identifying a ligand compound which binds to a cell membrane transporter, as recited in claim 64.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The claims contain only broad recitations of "ligands which binds to a cell membrane transporter". However, the instant specification does not provide to one skilled in the art a reasonable amount of guidance with respect to the

direction in which the experimentation should proceed in carrying out the full scope of the claimed methods. Note that the disclosure must be sufficient, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as claimed. *In re Vaeck*, 947 F.2d 488, 496 and n.23, 20 USPQ2d 1438, 1455 and n.23 (Fed. Cir. 1991). Therefore, due to the inadequacies of the instant disclosure, undue experimentation would be required of one of ordinary skill in the art to practice the full scope of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 64-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Portoghese**, (J. Med. Chem., 35 (11): 1927-1937 (1994); IDS filed 4/30/2002, ref. no. C11), **Joslyn et al.**, (J. Med. Chem., 31: 1489-1492 (1988); IDS filed 4/30/2002, ref. no. C7), and **Ackerman et al.**,(New England Journal of Medicine, 336(22): 1575-1586 (1997); IDS filed 4/30/2002, ref. no. C1).

Claims 64-68 are drawn to a method of preparing a library of compounds of the formula: L-X-L, wherein each L is independently a ligand which binds to a cell membrane transporter, wherein X is a linker of the formula –C(O)-alkylene-alkylene-C(O)-; the method comprising the steps of: (a) identifying a ligand compound which binds to a cell membrane transporter; (b) providing a plurality of functionalized ligands; (c) providing a linker comprising two reactive functional groups; (d) reacting the linker with the functionalized ligands to provide the library of compounds; further comprising assaying each compound of the library to determine the affinity of each compound for the cell membrane transporter; wherein the linker has a chain length between reactive functional groups of from about 2 to 100 ; wherein the cell membrane is an ion channel; and wherein the cell membrane transporter is a sodium ion channel. The claims are interpreted in light of the rejections under 35 U.S.C. 112, second paragraph.

Portoghese, (J. Med. Chem., 35 (11): 1927-1937 (1994); IDS filed 4/30/2002, ref. no. C11), at p. 1932, para 4 – p. 1935, para 2, particularly Fig. 6 and p. 1933, para 1, teaches methods of preparing a library of bivalent compounds of the formula: L-X-L, wherein each ligand is a naltrexone-derived pharmacophore that binds to an opioid receptor, wherein X is a spacer that is a linker of the formula –C(O)-R-C(O)-, wherein R is CH_2CH_2 or CH=CH; the method comprising the steps of: (a) identifying a ligand compound which binds to an opioid receptor; (b) providing a plurality of functionalized ligands; (c) providing a linker comprising two reactive functional groups; (d) reacting the linker with the functionalized ligands to provide the library of compounds; further comprising assay each compound of the library to determine the affinity of each

compound for the opioid receptor; and absent evidence to the contrary, wherein the linker has a chain length between reactive functional groups of from about 2 to 100 .

Portoghese does not teach ligands that bind cellular membrane transporters; wherein the cell membrane is an ion channel; and wherein the cell membrane transporter is a sodium ion channel.

Joslyn et al., (J. Med. Chem., 31: 1489-1492 (1988); IDS filed 4/30/2002, ref. no. C7), at the abstract and p. 1489, para 1 – p. 1491, para 2, teach methods of preparing a library of divalent compounds of the formula: L-X-L, wherein each ligand is a dihydropyridine that binds to a cell membrane transporter that is a calcium ion channel; the method comprising the steps of: (a) identifying a dihydropyridine ligand; (b) providing a plurality of functionalized ligands; (c) providing a linker comprising two reactive functional groups; (d) reacting the linker with the dihydropyridine to provide the library of compounds; further comprising assay each compound of the library to determine the affinity of each compound for the cell membrane transporter.

Ackerman et al.,(New England Journal of Medicine, 336(22): 1575-1586 (1997); IDS filed 4/30/2002, ref. no. C1) at p. 1576, Table 1, p. 1584, table 2, teach drugs that are ligands that bind to cellular sodium ion channel membrane transporters.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have combined methods for producing libraries of divalent ligand compounds comprising a linker of the formula –C(O)-alkylene-alkylene-C(O)-, (as taught by the reference of Portoghese), with methods for producing libraries of divalent ligand compounds that target cellular membrane transporters, (as taught by

reference of Joslyn), and wherein the ligands target sodium ion channel membrane transporters, (as taught by the reference of Ackerman).

One of ordinary skill in the art would have been motivated to use a linker of the formula –C(O)-alkylene-alkylene-C(O)-, because Portoghese (bridging paragraph pp. 1932-33) teaches the use of this linker as a spacer that permits varying spacer length, facilitates elaboration through standard peptide chemistry, avoids incremental increases in the hydrophobic properties upon lengthening, and introduces symmetry so as to connect as divalent ligands of calcium ion channel antagonists; and because Joslyn (p. 1489) teaches that such ligands are of proven value in treating cardiovascular disease and divalent ligands may enhance affinity by a minimum of twofold. One of ordinary skill in the art would have been motivated to use ligands that target sodium ion channel because the reference of Ackerman teaches drugs, including anticonvulsant and antiarrhythmic drugs, that target the sodium ion channels.

Conclusion

9. Claims 64-68 are rejected.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark L. Shibuya
Examiner
Art Unit 1639

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PRIMARY EXAMINER